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EXAMINER
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1652	

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23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/502,424	KILIAN ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-15,27-40,61,65,67-93 and 100-107* is/are pending in the application.

4a) Of the above claim(s) *7-10,30,33,35-40,68-70,86-91,100 and 102-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,11-15,27-29,31,32,34,61,65,67,71-85,92,93 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *27 March 2003* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *copies of sequence alignment* .

The Amendment and Reply under 37 CFR § 1.111 filed on March 27, 2003 as paper No. 20 and substitute specification filed on March 27, 2003 as paper No. 19 are acknowledged. The Amendments to the claims have been entered as requested. Claims 2 and 66 are cancelled; claims 1, 27, 32, 34, 61, 65, 71, 80, 81 and 101 are amended. Claims 1, 4-15, 27-40, 61, 65, 67-93 and 100-107 are pending.

Claims 1, 4-6, 11-15, 27-29, 31-32, 34, 61, 65, 67, 71-79, 80-85, 92-93 and 101are readable on the elected species of SEQ ID NO: 45 (amino acid SEQ ID NO: 46). Claims 1, 4-6, 11-15, 27-29, 31-32, 34, 61, 65, 67, 71-79, 80-85, 92-93 and 101 are the subject of this Office Action. Claims 7-10, 30, 33, 35-40, 68-70, 86-91, 100, 102–107 are withdrawn from consideration as directed to the nonelected invention.

Detailed Office Action

1. Objections

1.1. Specification

The objection to Table 1 on page 22 for lack of compliance with sequence rule is withdrawn because the amended Table 1 contains the sequence identification numbers for described variants.

The objection to the specification for lack of the nucleotide sequences of RTase motifs B, C and D is withdrawn, because the specification contains the description.

The specification is objected to for unclear description of motif A. On page 11, line 30 motif A is described as consisting of amino acids 708-720, which are 13 amino

acids. The sequence alignment, copy enclosed, shows that SEQ ID NO: 46 misses amino acids 711-722. On page 20, line 19 it is written that bases 2131-2166 are frequently spliced out and resulting protein is deleted for 12 amino acids, removing RTase motif A. Thus the specification is confusing as to the length of motif A and its location in SEQ ID No: 2.

Although Applicants write in their response:

> "Applicants have made every effort to comply with the Sequence Rules. It the Examiner is aware of any sequences which have not properly been identified, it is requested that the Examiner specifically point out these deficiencies" (page 4, line 17),

the specification still does not comply with sequence rules, because the primers quoted in descriptions of Fig. 8 and 9 on page 7 are lacking sequence identification numbers for the primers.

In addition, the appropriate sequence identification numbers are lacking on the following pages:

20, line 29;

21, line 19, 20, 22;

47, line 16;

48, line 5-9, 22, 29;

49, line 1, 4, 5, 9, 10, 15;

50, Table 2 lacks sequence identification numbers for the quoted oligomers;

56, line 24;

59, lack of sequence identification numbers for primers in the table and in line 25.

The specification is objected because Table 1 presents the exon/intron content of **ONLY** 32 splice variants, including the splice variant called by Applicant the reference protein. Splice variants of SEQ ID NOs: 35 and 52-54 toward which claims 4, 5, 34, 72 are directed are not present in Table 1. The extension of Table 1 is required so that it presents the intron/exon characteristics of all claimed splice variants.

Specification is objected to because in the Sequence listing SEQ ID NO: 35 is described as N-terminal truncated telomerase, whereas the sequence is not N-terminal-truncated but C-terminal-truncated. The protein is identical to residues 1- 588 of the reference protein of SEQ ID NO: 2. It is therefore unknown whether SEQ ID NO: 35 is an independent splice variant or a truncated form of the splice variant of SEQ ID NO: 2.

Specification is objected to because in the Sequence listing SEQ ID NO: 52 is described as N-terminal truncated telomerase, comprising intron Y, whereas the sequence is not N- terminal-truncated but C-terminal-truncated. Its length is 622 amino acids and identical to residues 1- 588 of the reference protein of SEQ ID NO: 2 having in position 75 an insert of 34 amino acids encoded by intron Y.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware.

1.2. Drawings

The examiner acknowledges corrections to Figures 11a-11u. The amended Figures are not correct; please note that amino acid residue 806 of SEQ ID NO: 39 is glycine. Newly filed SEQ ID NO: 39 still contains an error in amino acid residue 806; this error is reflected in Fig. 11. New corrected copies of Fig. 11a-11u are requested.

1.3. Claims

Claim 65 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). While wording differently, both claims appear to recite any splice variant of the human telomerase gene encoding SEQ ID NO: 2.

2. Rejections

2.1. 35 USC 112, second paragraph

Rejection Withdrawals

Rejection of claims 4, 5, 11-15 34; 71 and 72 made in the previous office Action, paper No. 18 is withdrawn because the correct amino acid sequence SEQ ID NO: 46 containing in residue No. 18 tyrosine was provided by Applicants.

Rejection of claim 27, 34, 61, 65, 71, 80 and 81 made in the previous Office Action, paper No. 18 is withdrawn because the claim has been amended.

The amended claim 1, 4, 11-15 and 101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "any of claims 1, 2, and 4-6. As claim 2 has been canceled, claim 11 has no antecedent.

The claims 1, 4, 11-15 and 101are confusing because they are directed to an isolated nucleic acid molecule encoding a splice variant of human telomerase of SEQ ID NO: 2. The term "a splice variant of human telomerase of SEQ ID NO: 2" is indefinite. There is no such thing as a splice variant of human telomerase of SEQ ID NO: 2, as SEQ ID NO: 2 is a protein produced from a messenger RNA which has already been spliced. There are splice variants of human telomerase and the protein set forth by SEQ ID NO: 2 is one of them. Any gene containing introns produces at least one splice variant and may have multiple splice variants, and in case of human telomerase reverse transcriptase the splice variant of SEQ ID NO: 2 in the instant Application or SEQ ID NO: 225 in Cech (II) happened to be identified first and for that reason is used by

Applicants and others as the reference protein. To examine the claim it is assumed that Applicant claim any splice variant of a human telomerase gene whose RNA is capable of being spliced to encode SEQ ID NO: 2.

Claims 1, 4, 65-67, 73-79, 101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite human splice variants. SEQ ID NO: 35 is described in the sequence listing as N-terminal truncated telomerase, whereas the sequence is not N-terminal-truncated but C-terminal-truncated. The protein is identical to residues 1- 588 of the reference protein of SEQ ID NO: 2. It is, therefore, unknown whether SEQ ID NO: 35 is an independent splice variant or a truncated form of the splice variant of SEQ ID NO: 2. As such the scope of then term "splice variant' is unclear.

Claim 65 recites the limitation "wherein the reference human telomerase gene" in the second line. There is insufficient antecedent basis for this limitation in the claim, because the claim does not recite a reference human telomerase gene.

2.2. 35 U.S.C. 112, first paragraph

2.2.1. Lack of written description

Claims 1, 4, 5-6, 11-15, 27, 61, 65-67, 73-79, 80-85, and 101 are rejected under 35 USC section 112 first paragraph for failing to provide sufficient written description. The rejection is explained in the previous Office Action, paper No. 18. It is reiterated herein that each of the members of the genus of splice variants has a unique structure.

In addition, the members of the genus have diversified functions. They may retain the telomerase function or lose it; and some of the variants may gain a new function. Applicants describe characteristic features of some of the variants on pages 20-21. For example, the splice variant of SEQ ID NO: 46 lost the telomerase activity. This protein functions in a dominant negative way causing cellular senescence and telomere shortening. A person skilled in the art recognizes that in the particular case of splice variants, none of the variants, or even tens of them, do not describe the structure and function other members of the genus, because one cannot establish only one function/structure relationship for the genus and thus the presence of a large number of species is still deemed to be not representative of the genus. Each new member necessarily has a different structure and many have distinct functions as well. Unless the specification could clearly associate each intron or exon structure with particular functions such that one skilled in the art could predict what the functional aspects of a new combination of the exons would be, the description of the structure and function of even a large number of members of the genus does not sufficiently describe the genus as the described members are not representative of the structure and function of not described members. Therefore, the specification has sufficiently described only those splice variants for which the complete structure is taught.

Applicants, in their response to rejection of claims 1, 4, 65-67 and 73-79 (paper No. 20) on page 7, line 19 write:

> "Applicants submit that they have taught 128 splice variants of human telomerase. See page 19,

line 14 to page 22, including Table 1, which includes seven alternatively spliced exons which are spliced in or out depending on the particular splice variant."

Applicants' argument has been fully considered but is found not persuasive for the following reasons. Applicants do not disclose 128 splice variants of human telomerase. The number 128 is a calculated maximal number of splice variants of any gene containing 7 introns. However, a splice variant is a naturally occurring protein. Merely because a particular arrangement is possible theoretically, does not mean it actually occurs in nature. Only those sequences which occur naturally are encompassed by the term "splice variant".

Table 1 does not include 128 splice variants but only 32, and there is no evidence to suggest the remaining theoretical combinations occur in nature. The table misses the splice variants of SEQ ID NO: 35 and 52-54 that are recited in the claim 4. SEQ ID NO: 35 is described in the sequence listing as N-terminal truncated telomerase, whereas the sequence is not N-terminal-truncated but C-terminal-truncated. The protein is identical to residues 1- 588 of the reference protein of SEQ ID NO: 2. It is therefore unknown whether SEQ ID NO: 35 is an independent splice variant or a truncated form of the splice variant of SEQ ID NO: 2. Sequence 52 is also described as N-terminal truncated, whereas it is a C-terminal truncated protein. As such it is unclear if these sequences are splice variants or not. Furthermore, Table 1 does not include seven, but six alternatively spliced intron/exon sequences.

Applicant also state,

"Applicants submit that the claims are directed to an isolated nucleic acid molecule that encodes a splice variant of human telomerase. The specification on page 8, beginning at line 10, teaches the genus of splice variants of human telomerase that are intended to be encompassed by the present invention. The species of the genus are the 128 splice variants that are taught by the present specification" (Page 7, line 24).

This argument is not found persuasive, because the genus of "splice variants of human telomerase" is likely substantially larger than 128 members (see below), and, as discussed above, even 35 disclosed splice variants are not representative of the variation of structure and functions of the entire genus. As stated in the guidelines "A representative number of species means that the species which are adequately described are representative of the entire genus." This is not the case here, as additional members of the genus necessarily have structures which are different than that of other members and will likely have different functions also, which functions are not predictable from the structure.

Applicants disclose 35 splice variants of SEQ ID NOs: 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82 and 84-86. Applicants realize that their disclosure of splice variants was not complete at the time the application was filed, because they have written on page 19, line 25 to page 20:

"**At least seven different putative introns appear to be** retained in mRNAs(see Figure 7, which displays 6 of 7 introns). The introns may be independently retained, a particular RNA may have none, any one, two, etc. up to seven introns. The maximum number of different mRNAs resulting from seven independently spliced introns is 2^7, or 128 different mRNAs. DNA sequences of these introns are presented in Figure 10. The 5'most intron, called sequence "X", is unknown length, and only a partial sequence is presented [emphasis MW]."

Furthermore, on page 22 one may read:

"The presence of the Y intron appears to cause a frameshift resulting in a truncated protein, but may cause an insertion [Emphasis added. Insertion of what? Are all possible inserts known and disclosed by Applicants? MW]"

Fig. 10 presents actually 8 intronic sequences set forth by SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, and Applicants claim all of them. Thus calculated number of splice variants given on page 19 should be 256, and not 128. Three of the intronic sequences, sequence 2 (SEQ ID NO: 29), X (SEQ ID NO: 32), and an intron whose partial sequence is that of SEQ ID NO: 33, are of unknown length, and, for that matter, structure. Thus, one cannot even predict the variants that are possible theoretically, because the structure of the entire genomic sequence of the telomerse reverse transcriptase gene is not presented in the specification. In summary, in spite of Applicant assertions, the claim(s) contain subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Currently the full genomic sequence of the human telomerase reverse transcriptase, hTERT, has been disclosed (Wick, et al, Gene, 1999, 232, 97-106, copy enclosed). The complete gene consists of 16 exons and 15 introns. Therefore, theoretically, the maximal number of independent splice variants should be 2^{15}, i.e., 32764. In addition, the length of introns currently numbered as 2, 6 and 12 is variable (Leem et al. Oncogene, 2002, 21, 769-777, copy enclosed), as these introns comprise tens of allelic forms. Also, the lengths of introns given by Wick et al. are not in accordance with those of the instant application, with exception for intron numbered currently 1, which is intron Y in the instant application. In conclusion, the complexity of structure and splicing of human telomerase is greater that that disclosed by Applicants at the early studies on the gene and its expression, therefore, the Applicants claim to all splice variants of human telomerase gene include subject matter not disclosed nor described in the specification.

Claims 5 and 11-15 remain rejected. The claims are directed to large genus of DNA molecules hybridizing to SEQ ID NO: 45. However, no function for the genus is stated and members of the genus would be functionally diverse including species encoding an active telomerase, encoding inhibitors of telomerase activity, species useful in diagnosis of the telomerase related disorders, and species which lack any

function. Addition of functional language would alleviate this rejection. Applicants argue that no functional recitation is necessary, because a sufficient number of species, which are representative of the genus have been described in the specification. This is not persuasive as the species are not representative of all the attribute and features of all members of the genus. Function is a highly important attribute of a compound, and, as previously detailed, the claimed genera will include members, which are highly variable in this feature. As such the disclosed species are not representative of the attributes and features of all members of the genus.

Claim 6 remains rejected. The claim is directed to a large genus of DNA molecules that hybridize to the complement of one of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33. The claimed genus lacks sufficient written description, because SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 are not representative species of said genus, as the claimed genus encompasses many members that are highly diverse both in the structure and function. The structure of DNA molecules selected by hybridization to SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 is very diversified. In addition, the claimed genus lacks functional characterization. Intronic sequences such as SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 do not have a specific biologic activity but may have use as diagnostic probes. However, the sequences selected by hybridization to the complements of intronic sequences may encode the telomerase reverse transcriptiase activity or other specific biologic activities. The telomerase reverse transcriptase activity is not encoded by the intronic sequences or their complements. Thus, the disclosed functions of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 are not representative of the

function of all members of the claimed genus. Therefore, claim 6 lacks both, structural and functional description.

Claim 61 remains rejected because the amended claim does not state the function of the isolated nucleic acid molecule comprising the sequence selected form the group: SEQ ID NO: 23, 25, 27, 29 or 30, or variants thereof which is 75% identical to all other variants of Fig 11 i.e., SEQ ID NO: 1, 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82 and 84-86, and members of this genus would be functionally diverse including species encoding an active telomerase, encoding inhibitors of telomerase activity, species useful in diagnosis of the telomerase related disorders, and species which lack any function. Addition of functional language would alleviate this rejection. Applicants argue that no functional recitation is necessary, because a sufficient number of species, which are representative of the genus have been described in the specification. This is not persuasive as the species are not representative of the attribute and features of all members of the genus. Function is a highly important attribute of a compound, and, as previously detailed, the claimed genera will include members which are highly variable in this feature. As such the disclosed species are not representative of the attributes and features of all members of the genus.

Claims 80-85 remain rejected because the claims are lacking written description of function and structure of large genus of the DNA molecules comprising SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 or variants of such molecules, or a large genus of DNA

molecules encoding any of the amino acid sequences of SEQ ID NOs: 24, 26, 28, and 31 or variants thereof.

The claims are directed to the extremely large genus of DNA molecules containing in their sequences those being of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33. The genus is lacking sufficient functional description. The specification does not contain disclosure of the function of all polynucleotides containing SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 or encoding SEQ ID NOs: 24, 26, 28 and 31. The claimed genus of polynucleotides is highly variable genus encompassing polynucleotides with a wide variety of functions including encoding an active telomerase, encoding inhibitors of telomerase activity, having diagnostic function and species which lack any function. The function of DNA molecules of SEQ ID NO: 18, 23, 25, 27, 29, 30, 32, 33, is to be used as a DNA probe for diagnostic purposes. However, the claims are directed to the genus of which all the species cannot be used as probes for diagnostic purposes. Other species have a variety of functions, which have not been described. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filled.

Applicant traverse rejection of claims 6, 61 and 80-85 for lack of written description emphasizing (page 9, line 31) that the claims are supported by adequate written description and further, that claimed members of the genera are related to each other structurally, and thus, fulfill the written description requirement.

The argument has been found non persuasive. As indicated above and reiterated here, the species set forth in the specification are not representative of all the

attributes and features of all members of the genus. Function is a highly important attribute of a compound, and, as previously detailed, the claimed genera will include members which are highly variable in this feature. As such the disclosed species are not representative of the attributes and features of all members of the genus.

Amending the claims to recite "an isolated nucleic acid consisting of a nucleotide sequence of SEQ ID NO: 18, 23, 25, 27, 29, 30, 32, 33" or "an isolated nucleotide sequence consisting of that encoding an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 26, 28, and 31" would overcome the instant rejection.

Claim 67 and 101 is rejected because the claim is directed to a genus of DNA molecules lacking the α insert (A motif) for which the structure characteristic is missing in the claim and the structure characteristics of motif A given in the specification is confusing; see the above objection to the specification. There are many variants of the telomerase gene of SEQ ID NO: 1 that are lacking the A motif but retain other introns. The specification teaches several such splice variants in Table 1, page 22, and the data presented indicate that Applicant possess at least 8 variants lacking the A motif, but the total number of such variants is probably greater.

In their response, page 10, line 17 Applicants argue,

"The examiner also asserts that the total number of variants lacking the A motif is 'probably greater' than that disclosed by the Applicants. OA at page 12. The Office has the burden of demonstrating lack of written

description. The examiner has not carried the burden because there are no facts to support the statement that the total number of variants lacking the A motif is 'probably greater' than that disclosed by the Applicants."

Applicants' argument has been fully considered but is found not persuasive. Maximal number of all splice variants calculated by Applicant is 128, i.e., Applicants assume that they have 7 introns. However Applicants disclose and claim 8 introns. Therefore the maximal expected number of splice variants would be 256. Introns of SEQ ID NO: 32, 29, 33, i.e., introns called by Applicants X, 2 and partial) are not disclosed in their entireties. That means that two splice variants having the same set of introns and exons and containing any of introns X, 2 and partial, may have different structure. Also, as indicated already above, the lengths of introns given by Wick et al. are not in accordance with those of the instant application, with exception for intron Y. Table 1 present 8 variants lacking the A motif, however the Table does not present splice variants wherein all 8 introns disclosed by Applicants are involved in splicing in or out. But even with six introns only, one can immediately observe that there is no splice variant with intronic configuration such as 0,0,0,0,0,0, or +, +, 0, 0, +, +. Thus, one skilled in the art can reasonably expect that Applicants did not disclose all splice variants missing intron α.

The splice variant of SEQ ID NO: 45 lost the telomerase activity and the protein functions in a dominant negative way causing cellular senescence and telomere shortening. There are 7 other species listed in Table 1 that are missing the α insert.

However, even these 8 representative species cannot provide identifying characteristics or properties other than being a gene encoding human telomerase splice variant lacking an A-motif, i.e., they cannot provide the structural and functional characteristics of the genus. Therefore, one skilled in the art is not convinced that Applicants had been in possession of the claimed invention at the time the application was filed.

2.2.2. Scope of enablement

Claims 1, 61, 65, 67, 73-79, 80-85 and 101 are rejected under 35 U.S.C. 112, first paragraph, for reasons stated in the previous Office Action, paper no. 18.

Claims 1, 65, 67, 73-79 and 101 remain rejected because the specification, while being enabling for the DNA encoding splice variant of human telomerase gene having SEQ ID NO: 45, as well as other 34 splicing variants of human telomerase including the reference SEQ ID NO: 2, is not enabling for any splice variant of human telomerase or any human telomerase splice variant that lacks RTase motif A, for reasons stated in the previous Office Action, paper no. 18, and addressed also in the above rejection for lack of written description.

Applicants in their response, page 11 line 10 write,

> "As stated above, the Applicants have discovered an extremely large number of splice variants of telomerase, and have given the sequence of each variant, along with the sequence of the alternatively spliced regions."

This arguments of Applicants have been fully considered, and is found persuasive in regards of SEQ ID NO: 1, 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82 and 84-86 but not in regards of any DNA molecule that comprises said molecules, or a variant thereof that is 75% identical to any of enumerated sequences, neither for a molecule that hybridizes to said molecules for reasons stated in the previous Office Action.

Claim 61, 80-85 remain rejected for scope of enablement because the specification, while being enabling for sequences consisting of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, is not enabling for any DNA molecule comprising a sequence from this group, or a complement or variant thereof, neither for a molecule that hybridizes to said molecules. The reasons are stated in the previous Office Action.

In their response to rejection made in the previous Office Action Applicants write the paragraph ***"Enablement rejection".*** Applicants attention is turn to the fact that the previous Office Action contains rejection for scope of enablement and not for total lack of enablement.

Applicants' opinion is,

"there was no analysis of these factors [Wand factors, MW] in the Office Action"(page 11 line 14).

While the previous Office Action did not address the Wands factors individually, the rejection discussed the pertinent factors within the body of the rejection. Below is a discussion of the Wands factors in even greater detail.

In part ***a. Nature of the invention*** Applicant state:

> "The invention is directed to splice variants of the human telomerase. The invention therefore involves the well known techniques of gene cloning, sequencing, expression, and testing the function of expressed protein. As the examiner has acknowledged, these techniques are highly developed. OA at page 15. Therefore, the nature of the invention is such that the state of the art, and the level of skill in the art are very advanced, and therefore, the splice variants of a human telomerase are enabled."

This quotation certainly indicates that the examiner analyzed the nature of the invention. However, the nature of the invention examined is substantially more complex than stated by Applicants in the above quotation. The claimed invention is not limited only to splice variant of human telomerase. The nature and breath of the claimed invention encompasses DNA molecule encoding any splice variant of human telomerase, or any human telomerase splice variant that lacks RTase motif, and any polypeptide comprising thereof, thus also non-naturally occurring variants. In addition, the claimed invention encompasses any DNA molecule comprising a sequence from group of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, or a complement or variant thereof. Thus, the clamed invention is of extreme complexity and many embodiments are unpredictable. For that reason, Applicants' argument,

"the nature of the invention is such that the state of the art, and the level of skill in the art are very advanced, and therefore, the splice variants of a human telomerase are enabled",

is not persuasive. The fact that skills of artisans are high does not mean that the full scope of the invention is enabled.

In part ***b. Breadth of the Claim*** Applicant state:

"There are a finite number of splice variants of human telomerase encompassed by the claim, Applicants have reduced to practice a large number of such variants and the claim is therefore not broader than the enabling disclosure of the specification."

The Applicants' arguments have been fully considered but are found not persuasive.

Even if the scope of the amended claim 1 and claim 65) is limited to splice variants of human telomerase, the scope of amended claims 61, and 80-81 is unchanged. Thus, the rejected invention comprises two genera: DNA molecules of splice variant of human telomerase and DNA molecules comprising sequence from the group of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, or a complement or variant thereof. The last genus comprises mostly DNA molecules that do not encode any splice variant of human telomerase. Thus, the invention is directed not only to DNA encoding splice variant of human telomerase.

The genus of polypeptide containing any of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, or a complement or variant thereof, encompasses mostly DNA molecules that are not splice variants, and these are clearly not finite in number. Furthermore, even for claims 1 and 65, in which the number of embodiments would clearly be finite in number, at the time of filling of the instant application it was not clear what this number was as the entire genomic sequence and the intron/exon structure of the human telomerase gene was not known. As previously discussed in written description rejection, even given the disclosure of the instant application it was clear that the claims encompassed substantially greater numbers of variants that 32 listed in Table 1 or 35 with known sequences that are claimed.

In addition, as discussed in the rejection for lack of written description, disclosing the structure of the 35 DNA molecules encoding splice variants of human telomerase is not a base for predicting the structure and function of other variants. Even if Applicants disclose 100 DNA molecules which are splice variants that does not provide the base for predicting the structure and function of remaining splice variants to the same extent as disclosing one splice variant only.

In part c. ***The State of the Prior Art and the Predictability of the Art*** Applicants conclude,

"The examiner has acknowledged that a large number of splice variants have been disclosed, yet has come to the illogical conclusion that the claim is not enabled, contrary to

the conclusion mandated by the case law and the MPEP [MPEP§2146.04, MW]."

This argument of Applicants have been fully considered but is found not persuasive for the following reasons.

MPEP§2146.04, quoting the case law, states:

> "According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement [emphasis added]. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments." and further
>
> "For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation [emphasis added]."

The following is examiner reasons for the uncertainty of the enablement.

Regarding claims 67 and 101 directed to splice variant lacking the A motif, Table 1 of the specification present 8 such variants. SEQ ID NO: 46 has the following configuration of intronic sequences; 0,0,0*,+,0,0 (0*means lack of the motif A).

The Table does not present splice variants wherein all 8 introns disclosed by Applicants are involved in splicing in or out. But even with six introns only, one can

immediately observe that there is no splice variant with intronic configuration such as 0,0,0*,0,0,0 or +, +, 0*, 0, +, +. Thus, one skilled in the art can reasonably expect that Applicants did not disclose all splice variants missing intron α, i.e., the A motif.

Regarding claims 1, 65 and 73-79 directed to any splice variant of human telomerase, maximal number of all splice variants calculated by Applicant is 128 (page 19), i.e., Applicants assume that they have 7 introns. However Applicants disclose and claim 8 introns set forth by SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33. Therefore the maximal expected number of splice variants should be 256. Introns of SEQ ID NO: 32, 29, 33, i.e., introns called by Applicants X, 2 and partial, are not disclosed in their entireties. That means that two splice variants having the same set of introns and exons and containing any of introns X, 2 and partial, may have different structure. Also, as indicated already above, the lengths of introns given by Wick et al. 1999 are not in accordance with those of the instant application, with exception for intron Y. These facts mean that complexity of structure and splicing of human telomerase is greater than that disclosed by Applicants at the early stage of studies on the gene and its expression. **Thus, information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation.**

The above presented state of the art certainly indicates unpredictability of the art regarding the structure and function of splice variants of human telomerase reverse transcriptase. Furthermore, Applicants' claims are vastly broader than just naturally occurring splice variants and encompass an enormous number of man-made variants

and fragments as well. Since the amino acid sequence of a protein determines its structural and functional properties, predicatability of which changes can be tolerated in a protein encoding sequence and obtain the desired activity requires a knowledge of which amino acids, if any, can be altered and which are intolerant to modification, as well as a detailed knowledge of how structure correlates to function. No such knowledge is present in the art regarding the human telomerase gene nor is it provided in Applicants' specification. Even if the knowledge of basic molecular biological techniques is high in the art, the lack of predictability of how alterations in structure of the disclosed variants would affect the function means that the Applicants have not sufficiently taught how to use the entire scope they are claiming without undue experimentation.

In part ***d. The presence or Absence of a Working example and the Amount of Direction or Guidance presented***, page 12, Applicants emphasize that example 1-5 teach in detail how to identify and isolate the claimed splice variants and state,

> "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the claimed genus could be used in that manner without undue experimentation."

However, this is, in fact, the point of the rejection. One could not expect that the undisclosed members of the genera claimed could be used without undue

experimentation in the same fashion as those exemplified. The specification though teaching a substantial number of working examples, does not priovide guidance for the skilled artisan to extend the teachings of those working examples to all members of the genera. The specification does not provide sufficient guidance for the skilled artisan with regard to how structure relates to function such that the skilled artisan could use the entire scope of what is claimed.

Also, Applicants attention is turn to the fact that lack of teaching examples was never raised by the examiner in her Office Action.

Applicants finish part ***d.*** writing:

> "The statement as a whole regarding the genus is that each one is a splice variant of telomerase, and splice variant of telomerase share common structural features."

Indeed, splice variant share considerable homology to each other, because they consist of fragments of genomic DNA. However predictability of the particular pattern of arrangement of these fragments in a particular variant is low, and the specification does not provide guidance for prediction of function of each new structure. In addition, the language of the claims is open, therefore the structure of claimed DNA molecules is almost unpredictable.

In part ***e. The Quantity of Experimentation Necessary***, page 13, referring to the examiner's statement that in the particular case of splice variants one skilled in the

art is unable to give a representative description of the genus, even if all members of the genus are identified and characterized, Applicants write:

> "This statement is false. There is a common trait to all splice variants because *by definition*, splice variants share common sequence [emphasis added]. The primary telomerase transcript, which is original unmodified RNA product of transcription of the telomerase gene, is the same for each of the splice variants. Therefore, reviewing the sequences of the splice variants reveals that there [is, MW] significant sequence which is common to all [emphasis added] of the splice variants. If this were not so, how would the inventors have known that the sequences were splice variants and not completely different proteins?"

Applicants arguments have been fully considered but are found not persuasive for the following reasons. **All splice variants do not share any specific common sequence. Splice variants do share fragments, introns and exons, of the primary transcript. However, it should be particularly noted that the primary transcript is NOT disclosed in the specification.** The set of fragments is not the same in each splice variant. Assuming that the telomerase gene has 7 introns one can calculate the maximal theoretical number of variants, and contemplate 128 patterns of arrangement (sets) of 8 exons and 7 introns. However, as discussed

above in rejection for lack of written description, not all of these arrangements occur in nature. In addition, currently is known that human telomerase gene consists of 16 exons and 15 introns, and that the introns are polymorphic. Thus, the number and variability of the possible arrangements of exons and introns is much greater that that exemplified by Applicants in their set of 35 splice variants.

In conclusion, examiners' statement that in the particular case of splice variants one skilled in the art is unable to give a representative description of the genus, even if all members of the genus are identified and characterized, is not false. The investor can readily identify a cDNA molecule as a splice variant because it contains a set of fragments of the primary transcript.

In summary, the claims lack enablement for the entire claimed scope as the claims are very broad, the art unpredictable, and the specification provides insufficient guidance in structure/function correlation, and thus the amount of experimentation necessary to make and use the entire scope claimed would be undue.

Finally, Applicants attention is turned to the fact that MPEP§2146.04 also states:

> " the examiner should always look for enabled, allowable subject matter and communicate to applicant what the subject matter is."

Accordingly, examiner, in the previous Office Action, suggested the amendments to the claims. It is reiterated here that any novel DNA molecules consisting of any of SEQ ID NO: 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74,

76-78, 80-82 and 84-86 and any of novel DNA molecules consisting of any of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 is allowable.

2.4. 35 USC section 102

Claims 1, 4, 6, 11-15, 61, 65, 73-79 and 80-85 were rejected in the previous Office Action as being anticipated by Cech et al in the US Patent No. 6,166,178 (Cech I) issued December 26, 2000, with priority to Oct. 1996 and US Patent No. 6,093,809 (Cech II) issued on July 25, 2000, with priority to Oct. 1996.

Rejection of any claim over Cech (I) is withdrawn because it was based on improper priority date.

Claim 1, 11-15, 65, 73-79, are directed to a DNA molecule encoding a splice variant of or human telomerase.

Claim 1 remain rejected as anticipated by Cech II, because Cech II disclose a splice variant of human telomerase of SEQ ID NO: 225 encoded by DNA molecule of SEQ ID NO: 224, which is the first splice variant of human telomerase ever described.

Claim 4 remains rejected as anticipated by Cech et al in the US Patent No. 6,093,809 issued on July 25, 2000, with priority to Oct. 1996. The claim is directed to the DNA molecule encoding a variant of SEQ ID NO: 46 that has at least 75% identity to amino acid sequence of SEQ ID NO: 46.

SEQ ID NO: 224 of the US Patent No. 6,093,809 encodes a variant of SEQ ID NO: 46 that has SEQ ID NO: 225 in the patent and has more than 75% amino acid identity to SEQ ID NO: 46; see the enclosed alignment.

Applicants, traversing this rejection write:

> "Applicants submit that SEQ ID NO: 225 is not a splice variant but rather the human telomerase reference protein. Therefore, the Cech patent does not anticipate the pending claims" (page 15, line 23).

This argument is not persuasive, because any protein encoded by a gene containing introns has splice variants, and in case of human telomerase reverse transcriptase the splice variant of SEQ ID NO: 2 in the instant Application or SEQ ID NO: 225 in Cech (II) happened to be identified as the first and for that reasons used by Applicants as the reference protein. Its use as the term "reference protein" in no way distinguishes it from other splice variants and nothing in the specification excludes it from the scope of this term either.

Claim 6, 11-15, 61 were rejected as being anticipated by Cech et al. in the US Patent No. 6,166,178, issued December 26, 2000, with priority to Oct. 1996 and the US Patent No. 6,093,809 ('809) issued on July 25, 2000, with priority to Oct. 1996.

The claims are directed to an isolated nucleic acid which will hybridize to a nucleic acid molecule comprising SEQ ID NO: 18, 25 and 27 or encoding amino acid sequence of SEQ ID NOs: 26 and 27and/or to fragments of these sequences.

Rejection over US Patent No. 6,166,178, is withdrawn.

Rejection of claims 6, 11-15 and 61 over US Patent No. 6,093,809 is not withdrawn. The patent discloses SEQ ID NO: 224 that contains in positions 2136-2221 the sequence identical to the whole sequence of SEQ ID NO: 25 of the instant application and in positions 2342-2523 the sequence identical to the whole sequence of SEQ ID NO: 27 of the instant application.

Applicants argue in their traverse: "SEQ ID NO: 224, is not a splice variant of human telomerase" (page 16, line 5).

This argument is not persuasive, because any protein encoded by a gene containing introns exists in splice variant forms, the fact well established before the application was filed. In case of human telomerase reverse transcriptase the splice variant of SEQ ID NO: 2 in the instant Application or SEQ ID NO: 225 in Cech (II) happened to be identified as the first and for that reasons used by Applicants and others as the reference protein.

Claims 27-29, 31-32, 34, 80-85 and 92 were rejected as being anticipated by Cech et al in the US Patent No. 6,166,178, issued December 26, 2000, with priority to Oct. 1996 and the US Patent No. 6,093,809 ('809) issued on July 25, 2000, with priority to Oct. 1996. Rejection over Cech et al. the US Patent No. 6,166,178 is withdrawn.

Claims 27-29 and 31 are directed to a nucleic acid probe that is specifically hybridizing to a nucleic acid molecule encoding a splice variant of human telomerase.

Cech et al. provide extensive disclosure regarding expression of telomerase, primers, hybridization, preparing oligonucleotide fragments of telomerase encoding DNA for the purposes of detecting the human telomerase gene product such as those detected by amplifying the gene and detecting amplification products. See US Patent No. 6,093,809, section *Uses of the Polynucleotides Encoding Telomerase Subunit Proteins*, column 32 line 30, list of primers in Table 3 in Example 18, column 58-59 of the US Patent No. 6,093,809). Cech et al. clearly suggests making such probes and primers from all regions of telomerase encoding nucleic acids, including exons and introns.

Oligonucleotides of US Patent 6,093,809, cover the following nucleotides of SEQ ID NO: 1 of the instant application:

SEQ ID NO: 99	1895-1913
SEQ ID NO: 87	1972-1990
SEQ ID NO: 92	2184-2202
SEQ ID NO: 89	2586-2682
SEQ ID NO: 88	2599-2617
SEQ ID NO: 94	3003-3021
SEQ ID NO: 96	3239-3257
SEQ ID NO: 95	3267-3285
SEQ ID NO: 96	3239-3257

SEQ ID NO: 97	3438-3454
SEQ ID NO: 98	3554-3571
SEQ ID NO: 90	3597-3615
SEQ ID NO: 91	3607-3625

Many of these oligonucleotides are hybridizing to many splice variants disclosed in the instant application. Particularly, SEQ ID NO: 45 hybridizes to all of the above listed oligonucleotides.

The properly chosen pairs from the primers of SEQ ID NOs: 87-99 if used, amplify splice junction of intronic sequences of the instant application that are different than SEQ ID NO: 18. For example, to amplify splice junctions for SEQ ID NO: 25 of the instant application oligomers of SEQ ID NO: 87 and 92 of Cech can be used. Therefore rejection of claims 27-29 and 31 is not withdrawn.

Claims 32 and 34 are directed to a pair of primers capable of specifically amplifying all or a portion of a nucleic acid molecule encoding a splice variant of human telomerase. Cech et al list in Table 3, column 58, of the US Patent No. 6,093,809, thirteen primers that were used to identify the human telomerase sequence; see the above list. The properly chosen pairs from the primers of SEQ ID NOs: 87-99 if used, amplify splice junction of intronic sequences of the instant application that are different than SEQ ID NO: 18. For example, to amplify splice junctions for SEQ ID NO: 25 of the instant application SEQ ID NO: 87 and 92 of Cech can be used. Therefore rejection of claim 32 and 34 is not withdrawn.

Claims 80-85 are directed to an isolated nucleic acid molecule comprising SEQ ID NO: 25 and 27 or encoding amino acid sequence of SEQ ID NOs: 26 and 27.

SEQ ID NO: 224 of US Patent No. 6,093,809 contains in positions 2136-2221 the sequence identical to the whole sequence of SEQ ID NO: 25 of the instant application. SEQ ID NO: 25 encodes the amino acid sequence of SEQ ID NO: 26.

SEQ ID NO: 224 of US Patent No. 6,093,809 contains in positions 2342-2523 the sequence identical to the whole sequence of SEQ ID NO: 27 of the instant application. SEQ ID NO: 27 encodes the amino acid sequence of SEQ ID NO: 28.

In conclusion, the rejection of claim 80-85 is not withdrawn.

Claim 92 is directed to a pair of oligonucleotide primers that amplify sequence of human telomerase containing a splice junction, wherein the primer pair flanks nucleotide 1950, 2131-2166, 2287-2468, 2843 or 3157. Those skilled in the art may properly chose pairs of oligonucleotide from the list above which originates from Cech II, Table 3, and use them to amplify the sequence of human telomerase that contain splice junction for example for intron 1 (1950) SEQ ID NOs: 99 and 87, alpha (2131-2166) SEQ ID NOs: 87 and 92.

Applicant is advised that any primer or a pair of primers identified by Applicants by it sequence identification number will be allowed when novel. Sets of primers are

quoted for example, in description of Fig. 8 and 9, and Table 2 gives a long list of primers together with their nuclotide sequences.

2.4. 35 USC section 103

Rejection of claim 93 made in the previous Office Action, paper No 18, is withdrawn because it is not anticipated by the US Patent No. 6,166,178 issued to Cech (Cech I), and because the Applcants' arguments regarding lack of motivation for use DNA fragment from Adam's paper are found persuasive.

2. 5. Double patenting

Obviousness type provisional double patenting is not withdrawn, because Applicants have elected to defer addressing this question until the claims of the copending application are held patentable.

3. Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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